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Hyperprolactinemia with Aripiprazole: a Case Report and Review of the Literature

Ayşe Nur İnci Kenar¹, Gulfizar Sozeri Varma¹

ÖZET:

Aripiprazol ile hiperprolaktinemi: Olgu sunumu ve literatür derlemesi

Hiperprolaktinemi antipsikotik tedavinin önemli, fakat ihmal edilebilen bir yan etkisidir. Aripiprazol dopamin D2 reseptörleri üzerinde parsiyel agonist etkili ve düşük hiperprolaktinematik yan etkiye sahip atipik bir antipsikotiktir. Bu olgu bildiriminde, psikotik özellikli depresyon tanısı konan ve plazma prolaktin seviyesi aripiprazol ile tedavi edilirken yükselen bir kadın hasta sunuldu. Aripiprazolün prolaktin yüksekliği yapma riskinin daha düşük olduğu bildirilse de klinisyenler aripiprazolün ılımlı prolaktin yüksekliği yapabileceğini göz önünde bulundurulmalıdır.

Anahtar sözcükler: aripiprazol, antipsikotik, hiperprolaktinemi, yan etki

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ABSTRACT:

Hyperprolactinemia with aripiprazole: a case report and review of the literature

Hyperprolactinemia is an important but often a neglected side effect of antipsychotic treatment. Aripiprazole is one of the new atypical antipsychotics that has partial agonist effects on dopamine D2 receptors and has a low possibility of hyperprolactinemia. In the present case report, we discuss a female patient who was diagnosed as suffering from depression with psychotic symptoms. Her prolactin levels were elevated while on treatment with aripiprazole. Clinicians should consider that aripiprazole may result in moderate elevation of prolactin levels although it is reported that it has a lower risk of elevation of prolactin levels.

Keywords: aripiprazole, antipsychotic, hyperprolactinemia, side effect

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INTRODUCTION

Hyperprolactinemia is an important but often a neglected side effect of antipsychotic treatment. Blockage of dopamine in the tuberoinfundibular dopamine system causes hyperprolactinemia¹. Dopamine inhibits prolactin release by stimulating D2 receptors and serotonin induces prolactin release by 5HT-2A receptors. Atypical antipsychotics do not effect dopamine blockage to the same extent as other antipsychotics in the tuberoinfundibular pathway, and inhibit prolactin release by mainly acting on serotonin by blocking 5HT-2A receptors¹⁻⁴.

Aripiprazole is a partial agonist of presynaptic and postsynaptic dopamine D2 receptors and has

a strong affinity for D3 receptors and moderate affinity for D4 receptors. It also acts as a partial agonist of serotonin 5HT-1A and 5HT-2C receptors, and an antagonist of 5HT-2A receptors. Consequently, it has been reported that the receptor binding profile of aripiprazole suggests efficacy on both positive and negative symptoms with a low risk of side effects, and it does not affect serum prolactin levels and it may even stabilize these levels^{5,6}.

In this case report, we present a female patient using antidepressants for depression with psychotic symptoms, who developed hyperprolactinemia when aripiprazole is added to the treatment and we discuss the effects of aripiprazole on serum prolactin levels.

CASE REPORT

A female patient, aged 21 years old, was referred to the psychiatry clinic with depressive complaints. She was diagnosed as having “major depressive disorder” according to the DSM-IV-R and sertraline 50 mg/day was prescribed and she has used the drug for 9 months. During the follow-up period, visual, aural hallucinations and persecution delusions developed compatible with her mood. Finally, she was diagnosed with major depressive disorder with mood-congruent psychotic features according to the DSM-IV-R and aripiprazole 10 mg/day was added to the treatment. During the follow-up period of 3 months; her depressive complaints were decreased and psychotic symptoms disappeared.

By the third month of aripiprazole treatment, she had hirsutism, amenorrhea and galactorrhea complaints. It was also learnt that she was being followed-up at the gynecology clinic because of polycystic ovary syndrome which has been in remission for 18 months with no drug treatment. When her clinical records were examined, her serum prolactin level (16.09 ng/ml, normal ranges 4-20 ng/ml) and testosterone level (74.9 ng/dl, normal ranges 0-80 ng/dl) were within normal ranges before aripiprazole treatment. Laboratory tests were repeated and her serum prolactin level was 27.14 ng/ml and testosterone level was 105 ng/dl. The increased level of serum prolactin was thought to be related to aripiprazole by the gynecology clinic and the drug was discontinued. In the control visit one month after the drug

discontinuance, serum prolactin (9.57 ng/ml) and testosterone (74.8 ng/dl) levels were found to be back to the normal levels and in the psychiatric examination, depressive symptoms were found to be increased and psychotic symptoms were found to have recurred. Thus, antidepressant treatment was continued and another atypical antipsychotic was prescribed.

DISCUSSION

Aripiprazole is known as a dopamine stabilizing agent. It has D2 receptor agonist and 5HT2A receptor antagonist properties. Based on these properties, it is reported that aripiprazole does not increase prolactin levels and may even decrease high prolactin levels associated with the use of other antipsychotics^{7,8}. However, it has been reported that prolactin levels increased to 30 ng/ml and up to twice normal levels in two studies performed with rats given aripiprazole^{4,9}. In these studies, high serum prolactin levels were interpreted as the mixed agonist/antagonist activity of aripiprazole on D2 receptors in lactotrop cells depending on the tonus of the existing dopaminergic neuronal activity. In other words, it was reported that the effect of aripiprazole resulted from its partial agonist property and its incomplete block of dopamine D2 receptors inhibiting prolactin release⁴.

There are a few case reports of hyperprolactinemia with aripiprazole. In the first report, a 36-year-old patient was receiving aripiprazole as monotherapy for schizophreniform

Table 1: Cases of hyperprolactinemia occurred with aripiprazole treatment

No	Authors	Diagnosis	Dose of aripiprazole	Duration of aripiprazole treatment	Drugs simultaneously used with aripiprazole
1	Mendhekar and Andrade (2005)	schizophreniform disorder	15 mg/day	three weeks	—
2	Ruffatti et al. (2005)	schizoaffective disorder	15 mg/day	a few days	haloperidol, sodium valproate, biperidene
3	Saraf et al. (2012)	bipolar affective disorder	15 mg/day	three months	lithium
4	Present case	depression with psychotic symptoms	10 mg/day	three months	sertraline

disorder, and aripiprazole dosage was increased from 10 to 15 mg/day in 2 weeks. Breast tenderness and galactorrhea appeared in the third week¹⁰. In another case, it was reported that breast tenderness and galactorrhea appeared in a few days while haloperidol was tapered as recommended and aripiprazole 15 mg daily was introduced in a 29-year-old patient for schizoaffective disorder. The patient had also been treated with sodium valproate 1000 mg and biperidene 4 mg for many years¹¹. In the last case, an 18-year-old patient was started on aripiprazole up to 15 mg/day with lithium 900 mg/day for bipolar affective disorder with a current episode of mania. On follow-up after 3 months, it was reported that she had complaints of oligomenorrhea and hyperprolactinemia¹² (Table 1).

The current patient had been diagnosed with depression with psychotic symptoms and was receiving a combination of aripiprazole and sertraline treatment. Sertraline, which is a member of the antidepressant group of selective serotonin reuptake inhibitors (SSRI), increases serotonin release, leads to a decrease of 5HT₂ receptors by desensitization of presynaptic 5HT-1A receptors and slightly blockades the reuptake of dopamine. Within this action profile, it has been reported that aripiprazole can cause hyperprolactinemia even if it is rare¹³. However, serum prolactin levels were normal while our patient was taking sertraline as monotherapy. Complaints due to hyperprolactinemia appeared when aripiprazole

was added to the treatment.

Aripiprazole daily doses (15 mg/day) in the aforementioned three literature cases were higher than the present case (10 mg/day). It is known that there is a linear relationship between the dose of aripiprazole and D₂ receptor occupancy¹². Hence, aripiprazole at lower doses has greater partial agonistic activity, and at higher doses, it possibly acts as a full D₂ antagonist. Therefore, it is more likely that hyperprolactinemia would occur in the previous case reports rather than in our case. It is noteworthy that the present case was taking an antipsychotic drug for the first time and its dose was low.

The patient has comorbid polycystic ovary syndrome and it may be a risk factor for hormonal dysregulation. However, the patient was regarded as being in remission for polycystic ovary syndrome at the end of the gynecology consultation. Although she tends to have hormonal dysregulation, it is thought that the hyperprolactinemia was caused by aripiprazole, because serum prolactin levels elevated with aripiprazole use and disappeared on drug discontinuance. Therefore, further investigation was not needed to rule out the other factors such as prolactinoma.

Consequently, clinicians should consider that the use of aripiprazole might result in elevation of serum prolactin levels, especially in polypharmacy and in risky patients such as those suffering from hormonal dysregulation, even though it has been reported to have little risk of hyperprolactinemia.

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